REMARKS

Claims 1-18 are presently pending in the instant Application. In the instant Amendment, Applicants have added new Claims 19-22, and have amended Claims 2, 4-11, and 13-18 merely to provide the Claims with a more appropriate format. Support for new Claims 19-22 as well as amended Claims 2, 4-11 and 13-18 can be found generally throughout the instant Specification, and particularly at page 3, lines 24-31; page 5, lines 8-10, and in Claims 1-16 as filed.

Applicants also file herewith a Request for Continued Examination (RCE) and a Supplemental Information Disclosure Statement.

The Invention is Novel

Claims 12 and 13 have been rejected under 35 U.S.C. § 102(b) as being anticipated by the teachings of U.S. Patent 4,810,488 (the '488 patent). The Examiner has asserted the '488 patent teaches a crystalline material with a reduced particle size of 2 to 5 microns, wherein the material is an anti-inflammatory steroid. Thus, the Examiner believes the teachings of the '488 patent anticipate Claims 12-13 of the instant Application.

Applicants respectfully traverse this rejection. As the Examiner is aware, the instant Application discloses and claims, *inter alia*, crystalline material containing substantially no amorphous content and having a median particle size of less than 2 microns Yet, the '488 patent is silent with respect to the amorphous content of the micronized product described therein. In particular, in col. 2, lines 27-36 of the '488 patent, it is explained that a crystalline solvate of an anti-inflammatory steroid, e.g. beclomethasone dipropionate, is produced. Subsequently, the crystalline solvate is dried and micronized to the desired particle size. Moreover, Example 1 in col. 3, lines 9-25 of the '488 patent makes clear that after the crystalline solvate is filtered and vacuumed, it is "...ground to a powder in a pestle and mortar and micronised in a Trost fluid

energy mill." Importantly though, it is not taught or implied in the '488 patent that the resulting micronized material possess substantially no amorphous content. MPEP § 706.02 makes clear that "...for anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." Since there is no teaching in the '488 patent that expressly or impliedly explains that micronized particles described therein contain substantially no amorphous content, then contrary to the Examiner's assertions, Claims 12-13, as well as Claims dependent thereto are clearly novel with respect to the '488 patent, and should be allowed to issue.

The Invention is Unobvious

Claims 12 and 13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the '488 patent. Although the Examiner has admitted the '488 patent does not specifically teach particles having a median particle size of 1 or 2 microns, the Examiner believes the '488 patent teaches a particle size range to be below 10 microns, and preferably 2 to 5 microns. However, as explained above, the '488 patent provides no teaching that the micronized particles described therein contain substantially no amorphous content. More importantly, the '488 patent teaches or suggests ***nothing*** with respect to the deleterious effects an increased amorphous content can have on the delivery of a drug and the potency of the drug, or even a desire to produce micronized drug particles having substantially no amorphous content to overcome such effects. Hence, contrary to the Examiner's assertions, the subject matter of Claims 12-13, as well as of Claims dependent thereto, is clearly unobvious to a skilled artisan in light of the teachings of the '488 patent, and Claims 12-22 should be allowed to issue.

Furthermore, Claims 1-16 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of U.S. Patent 3,897,010 (the '010 patent) in view of the

teachings of U.S. Patent 4,767,612 (the '612 patent) alone, or further in view of the teachings of U.S. Patent 6,145,765 (the '765 patent). The Examiner has admitted the '010 patent does not expressly teach: (1) that material to be milled is triamcinolone acetonide; and (2) that the inert gas used therein is helium. However, the Examiner has asserted the '010 patent teaches a method of milling material in which a fluid energy mill is employed to micronize the material, and the fluid is an inert gas at low temperature. The Examiner also believes the '010 patent teaches that the temperature of the fluid used lies in a cryogenic range or a range of the liquefication temperatures of the inert gas, and that the purpose of the low temperature is to bring the milling material to a low temperature in order to embrittle the material and facilitate pulverization in the fluid energy. It is the Examiner's position that the temperature of the fluid is reduced to a point such that the material to be milled is no longer plastically or elastically viscous but ruptures upon impact with a surface or another particle.

The Examiner has also asserted that the '612 patent teaches the micronization of triamcinolone acetonide in a fluid energy mill, wherein the particle size range of the micronized triamcinolone acetonide is from 1 to 5 microns. In making this rejection, the Examiner has admitted the '612 patent does not provide the complete temperature range at which triamcinolone acetonide is milled. Yet, the Examiner believes that differences in temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicated such temperature is critical. Moreover, citing *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955) for support, the Examiner contends that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

In light of the Examiner's assertions described above, the Examiner is of the opinion that at the time the instant Invention was made, it would have been obvious to a person of ordinary skill in the art to mill triamcinolone acetonide in a fluid energy mill at low temperatures to a mean particle size of 2 microns. It is also the Examiner's belief that one of ordinary skill in the art would have been motivated to mill at low temperatures in order to embrittle the milled material to be comminuted, which the Examiner has asserted results in a substantial increase in the throughput of the apparatus for a given energy, and in turn provides a substantial increase of efficiency. Hence, it is the position of the Examiner that the instant Invention as whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant Invention was made.

Moreover, the Examiner has asserted that the '765 patent teaches that an inert gas can be used as the fluid for a fluid energy mill, and that the inert gas can be helium. Hence, it is also the Examiner's position that one of ordinary skill in the art would have been motivated to combine the teachings of the '010, '612, and '765 patents, and thus choose a gas that is compatible with the material being processed, and which does not degrade the material upon contact with the fluid, e.g. helium.

Applicants respectfully traverse these rejections, and submit that no motivation or suggestion exists in any of these references to combine them as the Examiner has done in making these rejection. As the Examiner has admitted, the '010 patent teaches the micronization of material (not triamcinolone acetonide) in a fluid energy mill wherein the driving gas used is cooled until it condenses into a liquid. Indeed, it is clearly explained in col. 4, lines 19-30 of the '010 patent that:

> Still another feature of the present invention resides in the cooling of the driving-gas stream in a plurality of stages, for example

> including an initial stage in which it is cooled by heat exchange with the expanded cold gas stream to a low temperature and a second stage in which externally supplied cold brings the gas to still lower temperatures, e.g., in the cryogenic ranges ("lowest temperatures"). The term "cryogenic temperature" or "cryogenic range" is intended to refer to temperatures in the range of the ***liquification temperatures of such gases*** such as argon and other inert gases, nitrogen, oxygen, or therebelow.

(Col. 4, lines 19-30 of the '010 patent (emphasis added)).

In stark contrast, Claim 1 of the instant Application is directed towards a method for producing a fine, highly crystalline material product that comprises fluid energy milling a crystalline material using a milling fluid comprising helium, wherein the temperature of the milling fluid is between ***-30° C and -120° C***. Since the boiling point of helium is –268.6° C (approx. 4 K), ***it is impossible for helium used in a method of pending Claim 1 to be in a liquefied form***. Thus, the '010 patent, which requires a ***liquefied*** fluid, actually ***teaches away*** from Applicants' Invention.

Combining the teachings of the '010' patent with the '765 patent does not overcome the extreme disparity between the instant Invention and the teachings of the '010 patent. In particular, the '765 patent is silent with respect to the temperature at which milling with an inert gas, e.g. helium would be performed and specifically states that the fluid used in the energy mill described therein is a "gaseous fluid" (col. 2, line 15 of the '765). Thus, contrary to the Examiner's beliefs, no motivation or suggestion is present in either the teachings of the '010 or '765 patents for one of ordinary skill in the art to combine their teachings as the Examiner has done in making this rejection.

In addition, none of the art cited by the Examiner in these rejections teaches the production of ***crystalline*** particles having a size range of less than 10 microns. As the Examiner is readily aware, a method of the instant Invention produces a fine, highly crystalline material

product. Yet, the only comment made with respect to the condition of the final product produced pursuant to a method disclosed in the '010 application is set forth in col. 3, lines 12-13, wherein it is explained that "In some cases the embrittlement of the material itself may produce fragmentation." It is possible that such fragmentation would possess a substantial amorphous content, which is clearly contrary to the instant Invention. Likewise, the '612 patent is silent with respect to whether the micronized triamcinolone acetonide described therein is crystalline or amorphous.

In light of huge disparities among the teachings of the respective prior art cited by the Examiner, and with the instant Invention, it is respectfully submitted none of these references provides a motivation or suggestion to one of ordinary skill in the art to combine their teachings as the Examiner has done in making this rejection. Indeed, it appears that ***Applicants' disclosure*** has provided the Examiner with the motivation to combine these references in an unsuccessful attempt to reconstruct Applicants' Invention. Thus, the Examiner has impermissibly utilized hindsight in an unsuccessful attempt to reconstruct Applicants' Invention from this combination of references. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure." [*Interconnect Planning Corporation v. Fed.,* 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.,* 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). In the light of the above, it is respectfully submitted that this rejection be withdrawn, and the Claims be allowed to issue.

Change of Attorney/Agent

Applicants request that future communications regarding this Application be directed to the following:

Ross J. Oehler, Esq.
Aventis Pharmaceuticals Inc.
Patent Department
Route 202/206
P.O. Box 6800, Bridgewater, NJ 08807-0800
908-231-4000 (Tel.)
908-231-2626 (Fax)

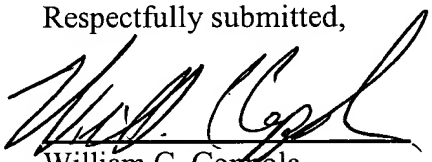
Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



William C. Coppola
Registration No. 41,686

AVENTIS PHRAMACEUTICALS INC.
Route 202-206; Mail Code: D-303A
P.O. Box 6800
Bridgewater, NJ 08807